REPORT ON BIOEQUIVALENCE STUDY

(Protocol No.: BEQ-464-MONT-2009, Version No.: 03, Date: 16th June 2011)

Study Title:

Bioequivalence study of single dose Montelukast sodium chewable tablets 5 mg (each chewable tablet contains montelukast sodium 5.2 mg equivalent to montelukast 5 mg) manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Singulair® (montelukast sodium) chewable tablets 5 mg (each tablet contains 5.2 mg montelukast sodium equivalent to 5 mg montelukast) distributed by Merck & Co. Inc., USA in healthy, adult, human subjects under fed condition.

Study Design:

An open label, balanced, analyst blind, randomized, two-treatment, two-period, two sequence, single dose, crossover bioequivalence study on 30 healthy, adult, human subjects under fed condition.

Investigational Product Details			**Dose**
i) Test Formulation (T)	:	Montelukast sodium chewable tablets 5 mg, Macleods Pharmaceuticals Ltd., India	1 x 5 mg
ii) Reference Formulation (R)	:	Singulair® (montelukast sodium) chewable tablets 5 mg, Distributed by Merck & Co. Inc., USA	1 x 5 mg

Duration of Clinical Phase	:	13th July 2011 – 08th August 2011
Duration of Bioanalytical Phase	:	18th August 2011 – 08th September 2011
Duration of Statistical Phase	:	14th September 2011 – 15th September 2011
Report Status	:	Final
Version	:	01
Dated	:	19th September 2011
Supersedes Version	:	None
Dated	:	Not Applicable

Sponsor	**Study Centre:**
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Statement of Compliance: This study was conducted in compliance with ICH GCP including archiving of essential documents.

Principal Investigator : Dr. Ashok Moses

Study Director : Dr. Ashish Mungantiwar

Sponsor's Representative : Mr. Amol Choulwar

2.0 SYNOPSIS OF THE REPORT

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Montelukast sodium chewable tablets 5 mg **Name of Active Ingredient:** Montelukast sodium	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

Title of Study: Bioequivalence study of single dose Montelukast sodium chewable tablets 5 mg (each chewable tablet contains montelukast sodium 5.2 mg equivalent to montelukast 5 mg) manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Singulair® (montelukast sodium) chewable tablets 5 mg (each tablet contains 5.2 mg montelukast sodium equivalent to 5 mg montelukast) distributed by Merck & Co. Inc., USA in healthy, adult, human subjects under fed condition.

Investigator: Dr. Ashok Moses, Principal Investigator

Study Centre: Macleods Pharmaceuticals Ltd., Bioequivalence Department

Publication (reference): Not Applicable

Study period:

Date of Screening	:	30th June 2011 – 11th July 2011
Duration of Clinical Phase	:	13th July 2011 – 08th August 2011
Period 1	:	13th July 2011 – 15th July 2011
Period 2	:	20th July 2011 – 22nd July 2011
Duration of Bioanalytical Phase	:	18th August 2011 – 08th September 2011
Duration of Statistical Phase	:	14th September 2011 – 15th September 2011

Objectives:

i) Pharmacokinetic: To evaluate the comparative oral bioavailability of single oral dose Montelukast sodium chewable tablets 5 mg (each chewable tablet contains montelukast sodium 5.2 mg equivalent to montelukast 5 mg) manufactured by Macleods Pharmaceuticals Ltd., India with Singulair® (montelukast sodium) chewable tablets 5 mg (each tablet contains 5.2 mg montelukast sodium equivalent to 5 mg montelukast) distributed by Merck & Co. Inc., USA in healthy, adult, human subjects under fed condition.

ii) Safety: To monitor the safety and tolerability of a single oral dose of Montelukast sodium chewable tablets 5 mg when administered orally in healthy, adult, human subjects under fed condition.

Methodology: Serial blood samplings (pre-dose and at 0.33, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00 and 32.00 hours post-dose) were done before and up to 32.00 hours post-drug administration. Analysis of plasma samples for montelukast concentrations was done using an in-house validated LC-MS/MS method. A non-compartmental method was used to calculate pharmacokinetic parameters using drug concentration time profile. Statistical comparison of the pharmacokinetic parameters of both the formulations was done to assess bioequivalence.

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Montelukast sodium chewable tablets 5 mg **Name of Active Ingredient:** Montelukast sodium	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

Number of Subjects (planned and analysed):

A total of 30 subjects were planned and enrolled, of these 30 subjects, subject number 13 was withdrawn from the study in period 2 (post-dose) on principal Investigator's advice due to adverse event. Thus twenty-nine subjects completed both the periods. The data of twenty-nine completing subjects (01 to 12 and 14 to 30) were taken for pharmacokinetic and statistical evaluations.

Diagnosis and main criteria for inclusion:

Healthy human subjects within the age range of 18 to 45 years with body-mass index (BMI) between 18.50 kg/m^2 and 29.99 kg/m^2 (both inclusive) with body weight not less than 50 kg (for males) and with body weight not less than 45 kg (for females) and having absence of significant disease, clinically significant laboratory values, absence of clinically significant medical history and normal physical examination during the screening and complying with inclusion and exclusion criteria were the criteria for inclusion.

Test Product (T): Montelukast sodium chewable tablets 5 mg (each chewable tablet contains montelukast sodium 5.2 mg equivalent to montelukast 5 mg)
Batch No.: BMD8102C
Manufacturing Date: MAY 2011
Expiry Date: APR 2013
Manufactured by: Macleods Pharmaceuticals Ltd., India
Dose: 1 tablet
Mode of administration: Administered orally with 240 mL of drinking water.

Reference Product: Singulair® (montelukast sodium) chewable tablets 5 mg (each tablet contains 5.2 mg montelukast sodium equivalent to 5 mg montelukast)
Lot No.: Z1257
Manufacturing Date: N/AV
Expiry Date: 09-2012
Distributed by: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ 08889, USA. NDC-0006-0275-31
Dose: 1 tablet
Mode of administration: Administered orally with 240 mL of drinking water.

Duration of Treatment	Single dose in both periods.

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Montelukast sodium chewable tablets 5 mg **Name of Active Ingredient:** Montelukast sodium	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

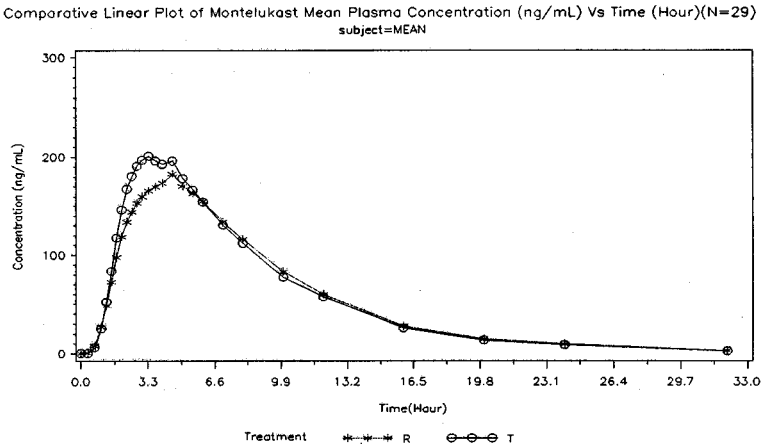
Criteria for Evaluation:

Efficacy: The 90 % confidence interval for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of montelukast formed the basis for concluding the equivalence of Montelukast in product R and T. If the confidence intervals are entirely included in the range of 80.00 – 125.00% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ log-transformed then the treatments would be claimed to be bioequivalent.

Safety: To monitor the safety and tolerability of a single oral dose of Montelukast sodium chewable tablets 5 mg when administered orally in healthy, adult, human subjects under fed condition.

Statistical Methods: The log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Montelukast are analysed using an ANOVA model. Calculated 90% confidence interval for the ratio of both the products averages (geometric means) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Ratios of mean AUC_{0-t} to mean $AUC_{0-\infty}$ for test and reference are expressed in percentage and power test is performed using SAS® version 9.2.

SUMMARY – CONCLUSION
EFFICACY RESULTS:



The 90 % confidence intervals of ln-transformed parameters for Montelukast summarized below:

Geometric mean, Ratio, Intra-Subject C.V., Power and 90 % Confidence Interval for Montelukast						
Pharmacokinetic Parameters	**Geometric mean**		**Ratio (T/R) (%)**	**Intra Subject C.V. (%)**	**Power (%)**	**90 % Confidence Interval (%)**
	Test (T)	**Reference (R)**				
C_{max} (ng/mL)	226.256	202.497	111.73	18.08	99.38	103.11 - 121.07
AUC_{0-t} (ng*hrs/mL)	1678.498	1620.421	103.58	8.85	100.00	99.57 - 107.76
$AUC_{0-\infty}$ (ng*hrs/mL)	1715.060	1657.176	103.49	8.86	100.00	99.48 - 107.67

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Montelukast sodium chewable tablets 5 mg **Name of Active Ingredient:** Montelukast sodium	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

SAFETY RESULTS:

One subject (subject number 13) experienced adverse event during conduct of the study. During post study safety assessment adverse events were reported for five subjects.

CONCLUSION:

The test product, Montelukast sodium chewable tablets 5 mg (each chewable tablet contains montelukast sodium 5.2 mg equivalent to montelukast 5 mg) manufactured by Macleods Pharmaceuticals Ltd., India is bioequivalent to the reference product, Singulair® (montelukast sodium) chewable tablets 5 mg (each tablet contains 5.2 mg montelukast sodium equivalent to 5 mg montelukast) distributed by Merck & Co. Inc., USA in healthy, adult, human subjects under fed condition. Both the formulations are well tolerated following a single dose administration of the investigational products.

Date of the Report: 19th September 2011.

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4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

µL	:	Microlitre
ANOVA	:	Analysis of Variance
AUC	:	Area under Curve
AUC_{0-t}	:	Area under the concentration versus time curve calculated using the Trapezoidal rule upto the last measurable time point
$AUC_{0-\infty}$	:	Area under the concentration versus time curve from time zero to infinity
BLQ	:	Below Limit of Quantification
BMI	:	Body Mass Index
B.P.	:	Blood Pressure
bpm	:	Beats Per Minute
CAP	:	College of American Pathologists
CBC	:	Complete Blood Count
CCF	:	Congestive Cardiac Failure
C_{max}	:	Concentration Maximum
COA	:	Certificate of Analysis
CPU	:	Clinical Pharmacology Unit
CV	:	Coefficient of Variation
^0C	:	Degree Centigrade
D	:	Day
ECG	:	Electro Cardiogram
EDTA	:	Ethylene Diamine Tetra-Acetic Acid
ESR	:	Erythrocyte Sedimentation Rate
GCP	:	Good Clinical Practices
GGT	:	Gama Glutamyl Transpeptidase
GMP	:	Good Manufacturing Practices
HbsAg	:	Hepatitis B Surface Antigen
HCV	:	Hepatitis C Virus
HIV	:	Human Immunodeficiency Virus
hrs	:	Hour(s)
I.D.	:	Identity
ICF	:	Informed Consent Form
ICH	:	International Conference on Harmonization
ICMR	:	Indian Council of Medical Research
IEC	:	Independent Ethics Committee
IP	:	Investigational Product
IU	:	International Unit
IUD	:	Intrauterine Device
K_{el}	:	Elimination rate constant
LC-MS/MS	:	Liquid Chromatography with Mass Spectroscopy/ Mass Spectroscopy

LFT	:	Liver Function Test
L/kg	:	liter / kilogram
L/h/kg	:	Lower Limit of Quantification
LSM	:	Least Square Means
ME	:	Medical Examination
Mg	:	milligram
mL	:	milliliter
NABL	:	National Accreditation Board for Testing and Calibration Laboratories
oz	:	Ounce
PCV	:	Packed Cell Volume
PK	:	Pharmacokinetic
QA	:	Quality Assurance
R	:	Reference Product
RBC	:	Red Blood Cell
RFT	:	Renal Function Test
RH	:	Relative Humidity
rpm	:	Revolution Per Minute
SAE	:	Serious Adverse Event(s)
SADR	:	Serious Adverse Drug Reactions
SAS	:	Statistical Analysis System
SGOT	:	Serum Glutamate Oxaloacetate Transaminase
SGPT	:	Serum Glutamate Pyruvate Transaminase
SOP	:	Standard Operating Procedure(s)
SQ	:	Subject Questionnaire
T	:	Test Product
$t_{1/2}$	:	Terminal Half-life
t_{max}	:	Time of maximum measured plasma concentration. If maximum value occurs at more than one point, T_{max} is defined as the first point with this value in each period
TG	:	Triglycerides
USFDA	:	United States Food and Drug Administration
w/v	:	Weight / Volume

5.0 ETHICS

5.1 Independent Ethics Committee (IEC)

The protocol, BEQ-464-MONT-2010, version no. 02, dated: 21st February 2011 and English ICF, version no. 02, dated: 21st February 2011 and Hindi and Marathi ICFs version no. 01 dated: 28th February 2011 were sent to IEC on 07th March 2011. The Independent Ethics Committee in its meeting held on 23rd March 2011 gave provisional approval.

Due to changes and few modifications, the protocol and ICFs were amended and thus the protocol, BEQ-464-MONT-2010, version no. 03, dated: 16th June 2011 and English ICF, version no. 03, dated: 16th June 2011 and Marathi and Hindi ICFs version no. 02 dated: 16th June 2011 along with COA were sent to IEC on 21st June 2011. The Independent Ethics Committee in its meeting held on 06th July 2011 gave final approval to the submitted protocol and ICFs.

Approval was granted after the review of documents and the approved version bears the following version number and date:

Protocol : Version No. 03, dated: 16th June 2011
English ICF : Version No. 03, dated: 16th June 2011
Hindi ICF : Version No. 02, dated: 16th June 2011
Marathi ICF : Version No. 02, dated: 16th June 2011

Dr. Mrs. K.C.P. Walawalkar chaired the IEC. The copy of the IEC approved protocol is appended as appendix 16.1.1. The details of IEC consulted along with approval letter and IEC approved ICFs are given in appendix 16.1.3.

The IEC summary report regarding the conduct of the study was sent to IEC on 09th August 2011.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the principles of the Declaration of Helsinki, 'ICH GCP', National Regulations (ICMR Guidelines), 'Indian GCP', USFDA guidelines and "Schedule Y" of Indian Drugs and Cosmetics Act.

5.3 Subject Information and Consent

Subjects from the pool of healthy volunteers who were screened within 21 days prior to the dosing day were considered as potential participants in the study. Before admission of volunteers into the Clinical pharmacology unit (CPU) on the pre-study day, they were given a verbal presentation of the information on the study together with a written document (in the language that they can understand best) describing the purpose, procedures, and risks of the study together with a description of the obligations of the subjects. Volunteers gave their written consent for participating in the study by signing with date the informed consent form. The signed copy of the form is kept in the study specific ICF file at the investigator's/institution site and the subjects were also given a copy for their own retention. A copy of the consent form used is appended in appendix 16.1.3. Before the volunteers undergo the pre-screening process for acceptance into healthy volunteer bank, they were provided with written and verbal information about the nature of the tests to be performed following which all willing volunteers gave their written consent.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

SPONSOR'S REPRESENTATIVE

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Deputy Manager – Medical Services

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BIOEQUIVALENCE DEPARTMENT PERSONNEL

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Principal Investigator:

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D) Bioanalytical Facility : Macleods Pharmaceuticals Ltd.,
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The list of investigators with their affiliations, their role in the study and their curriculum vitae are appended as appendix 16.1.4. The list of other important participants in the study is appended in appendix 16.1.4. The declaration statement by the principal investigator is appended as appendix 16.1.5.

7.0 INTRODUCTION

The cysteinyl leukotrienes (LTC4, LTD4, LTE4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 (CysLT1) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction and altered cellular activity associated with the inflammatory process. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis.

Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity.

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatics. [1]

Clinical Pharmacokinetics:

Absorption

Montelukast is rapidly absorbed following oral administration.

For the 5-mg chewable tablet, the mean Cmax is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady state volume of distribution of montelukast averages 8 to 11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

Metabolism

Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.

Elimination

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal

collections and < 0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (14%).

Gender Effect: The pharmacokinetics of montelukast are similar in males and females. [1]

Indications and Uses

Asthma

SINGULAIR is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

Exercise-Induced Bronchoconstriction

SINGULAIR is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older.

Allergic Rhinitis

SINGULAIR is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older. [1]

Adverse Reactions

The most common adverse reactions (incidence ≥ 5% and greater than placebo; listed in descending order of frequency) in controlled clinical trials were: upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis.

Adults and Adolescents 15 Years of Age and Older with Asthma

Adverse Experiences Occurring in ≥1% of Patients with an Incidence Greater than that in Patients Treated with Placebo

Body As A Whole: Pain, abdominal, Asthenia/fatigue, Fever, Trauma
Digestive System Disorders: Dyspepsia, Pain dental, Gastroenteritis, infectious
Nervous System/Psychiatric: Headache, Dizziness
Respiratory System Disorders: Influenza, Cough, Congestion nasal
Skin/Skin Appendages Disorder: Rash
Laboratory Adverse Experiences: ALT increased, AST increased, Pyuria

Adults and Adolescents 15 Years of Age and Older with Seasonal Allergic Rhinitis

In placebo-controlled clinical trials, the following event was reported with SINGULAIR with a frequency ≥1% and at an incidence greater than placebo: upper respiratory infection, somnolence.

Adults and Adolescents 15 Years of Age and Older with Perennial Allergic Rhinitis

The following events were reported with SINGULAIR with a frequency ≥1% and at an incidence greater than placebo: sinusitis, upper respiratory infection, sinus headache, cough, epistaxis, and increased ALT. The incidence of somnolence was similar to that of placebo. [1]

Precautions and Contraindications

PRECAUTIONS

Acute Asthma

SINGULAIR is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Patients should be advised to have appropriate rescue medication available. Therapy with SINGULAIR can be continued during acute exacerbations of asthma. Patients who have exacerbations of asthma after exercise should have available for rescue a short-acting inhaled β-agonist.

Aspirin Sensitivity

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR. Although SINGULAIR is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients.

Neuropsychiatric Events

Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Post-marketing reports with SINGULAIR use include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug-induced effect.

Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur.

Eosinophilic Conditions

Patients with asthma on therapy with SINGULAIR may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications and/or neuropathy presenting in their patients. A causal association between SINGULAIR and these underlying conditions has not been established.

Phenylketonuria

Phenylketonuric patients should be informed that the 4-mg and 5-mg chewable tablets contain phenylalanine (a component of aspartame), 0.674 and 0.842mg per 4-mg and 5-mg chewable tablet, respectively.

CONTRAINDICATIONS

Hypersensitivity to any component of this product. [1]

Study Rationale

The Macleods Pharmaceuticals Ltd. has developed generic alternative to the reference-listed brand of Montelukast sodium chewable tablets. Therefore, its bioequivalence with the reference brand must be evaluated in both fast and fed conditions. In the present study, the single dose of test product Montelukast sodium chewable tablets 5 mg (each chewable tablet contains montelukast sodium 5.2 mg equivalent to montelukast 5 mg) manufactured by Macleods Pharmaceuticals Ltd., India was compared with Singulair® (montelukast sodium) chewable tablets 5 mg (each tablet contains 5.2 mg montelukast sodium equivalent to 5 mg montelukast) distributed by Merck & Co. Inc., USA under fed condition.

Justification of Choice of Reference Product

Singulair® (montelukast sodium) chewable tablets 5 mg is qualified as acceptable reference listed drug in USFDA.

8.0 STUDY OBJECTIVES

The bioequivalence study presented here was carried out for evaluating the following objectives:

8.1 Pharmacokinetic:

To evaluate the comparative oral bioavailability of single dose Montelukast sodium chewable tablets 5 mg (each chewable tablet contains montelukast sodium 5.2 mg equivalent to montelukast 5 mg) manufactured by Macleods Pharmaceuticals Ltd., India with Singulair® (montelukast sodium) chewable tablets 5 mg (each tablet contains 5.2 mg montelukast sodium equivalent to 5 mg montelukast) distributed by Merck & Co. Inc., USA in healthy, adult, human subjects under fed condition.

8.2 Safety

To monitor the safety and tolerability of a single dose of Montelukast sodium chewable tablets 5 mg when administered orally in healthy, adult, human subjects under fed condition.

9.0 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

An open label, balanced, analyst blind, randomized, two-treatment, two-period, two sequence, single dose, crossover bioequivalence study on 30 healthy, adult, human subjects under fed condition.

ADMISSION AND STAY

Period 1:

On 13th July 2011, informed consent was presented to all the volunteers. At the time of check-in, eligibility was assessed by carrying out test for drugs of abuse, medical examination, confirming compliance to protocol based upon inclusion and exclusion criteria and recording vitals. Breath of the volunteer was analyzed to check the consumption of alcohol using breath alcohol analyzer. Thirty subjects who were found to be compliant with the requirements of the protocol were checked in Clinical Pharmacology Unit (CPU) between 16:30 hrs to 18:45 hrs.

During the in-house stay, monitoring of vital signs and subject questionnaire at the time of check-in, pre-dose and at 2.00, 5.00, 9.00 and 24.00 hours post-dose (Time points being relative to the investigational product dosing) was done. Medical examinations were carried out at the time of check-in and checkout.

All the subjects enrolled into the study were housed in the Clinical Pharmacology Unit (CPU) until checkout on 15th July 2011.

The subjects visited to the clinical facility for ambulatory blood sample collection at 32.00 hours post-dose.

Period 2:

On 20th July 2011, all subjects reported to the clinical facility. At the time of check-in, eligibility was assessed by carrying out test for drugs of abuse, medical examination, confirming compliance to protocol based upon exclusion criteria and recording vitals. Breath of the subject was analyzed to check the consumption of alcohol using breath alcohol analyzer. Thirty subjects who were found to be compliant with the requirements of the protocol were checked in Clinical Pharmacology Unit (CPU) between 18:06 hrs to 20:12 hrs.

During the in-house stay, monitoring of vital signs and subject questionnaire at the time of check-in, pre-dose and at 2.00, 5.00, 9.00 and 24.00 hours post-dose (Time points being relative to the investigational product dosing) was done. Medical examinations were carried out at the time of check-in and checkout of the study.

All the subjects were housed in the Clinical Pharmacology Unit (CPU) until checkout on 22nd July 2011.

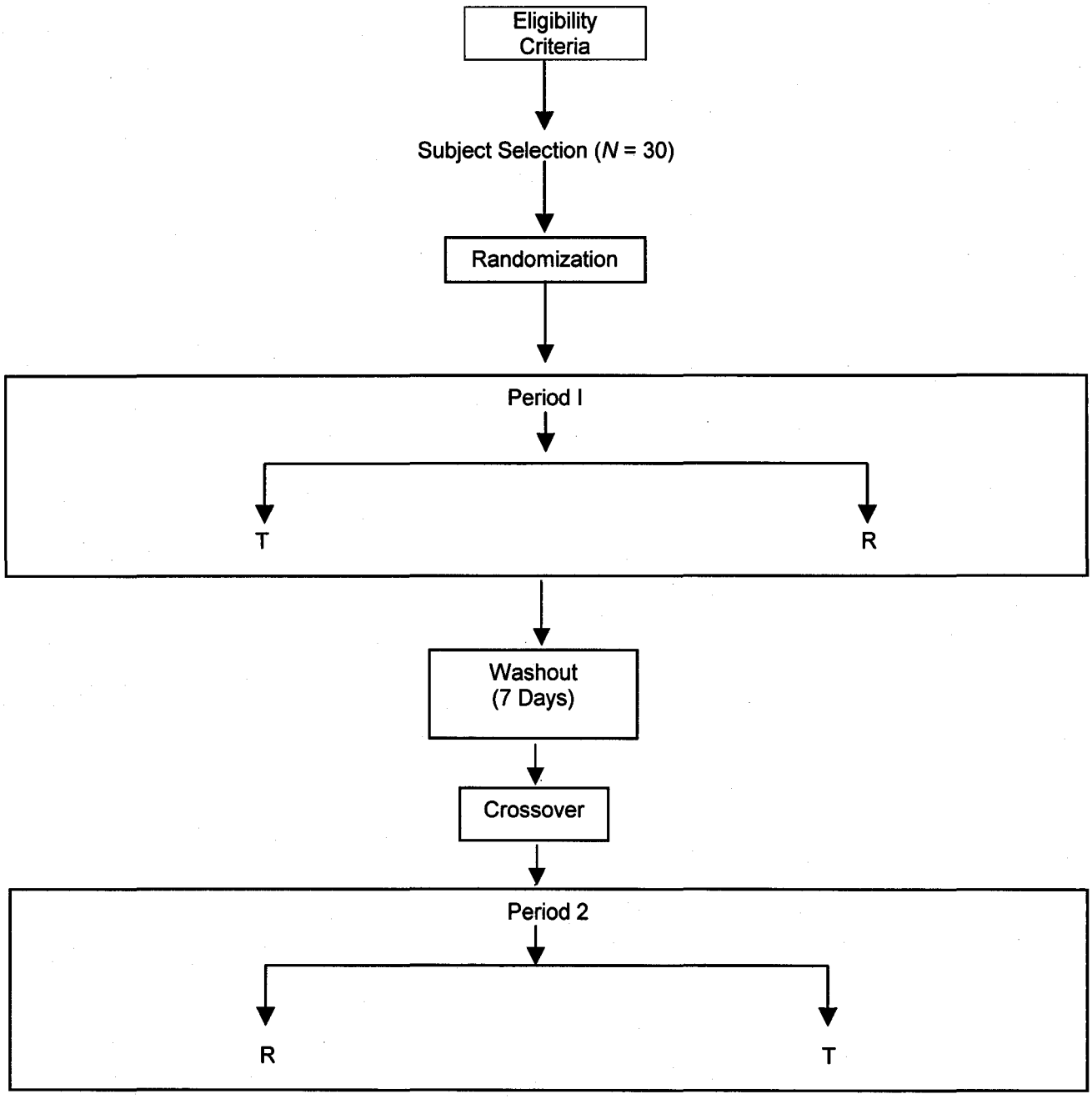
The subjects visited to the clinical facility for ambulatory blood sample collection at 32.00 hours post-dose.

Washout Period:

There was a washout period of 07 days from the completion of dosing between two consecutive periods.

The study schematic is given in figure-1 on next page.

FIGURE – 1 STUDY PLAN



N – Number of Subjects

R – Reference Product

T – Test Product

9.2 Discussion of Study Design, Including the Choice of Control Group

It was an open labeled study. The analysts concerned, however, were blinded to the sequence of administration of test and reference product to the individual subjects.

The order of receiving treatment was randomized to avoid bias in allocation of sequence to the subjects.

There were two treatments: the sponsor's product was the test product while the innovator product was the reference product.

The subjects served as their own control, the study being crossover.

Since there were two treatments, the trial design was two period, two sequence. The effect of period and sequence on primary efficacy criteria was analyzed by ANOVA (Analysis of variance).

To reduce variability in the biomedical experimentation and to control factors, which may affect the evaluation and comparison of primary efficacy factors; healthy, adult, human male subjects were selected.

The number of subjects to be included in the study was derived from the published literature. [2]

With the mean plasma half-life of Montelukast ranged from 2.7 to 5.5 hours, the two dosing days i.e. period 1 and period 2 were separated by a washout period of 7 days.

9.3 Selection of Study Population

The general screening was carried out after obtaining the written consent on IEC approved 'Informed Consent for Screening' from the volunteers. The screening procedure included Demographic data including sex, completed age, height and weight, Body Mass Index (BMI), diet, history of tobacco use, intake of abusive/recreational drugs, alcohol intake, history of blood donation and history of participation in a drug research study. Medical history, including relevant past medical / surgical history, family history, history of allergies (food / drug / any other), past medication history in the last 90 days. Medical examination including recording of vital signs (Blood Pressure (BP), Pulse, Respiration and Temperature), general examination, physical and systemic examination. 12-lead ECG for heart rate, rhythm and specific finding (if any). Chest X-ray (PA view); Laboratory parameter investigation including Complete complete blood count – Leucocyte count, Erythrocyte count, Haemoglobin, Hematocrit, Platelet count, differential leucocyte count (DLC); and ESR, Blood grouping (if previously not performed by Bioequivalence department of Macleods Pharmaceuticals Ltd.), Biochemistry – blood sugar (fasting), cholesterol and triglycerides, Alkaline Phosphatase, Hepatic Profile – SGPT, SGOT, GGT and Serum Bilirubin (Total, Direct, Indirect), Renal profile – serum creatinine, BUN, Serum Calcium, Serum Electrolytes (sodium, potassium. chlorides) and Infectious Diseases – HbsAg, HIV and HCV and routine urine examination.

No clinically significant abnormalities in ECGs, Chest X-ray (PA view) were reported in subjects who were included in the study. Additionally, serological tests (HIV, Hepatitis B and C, HCV) were negative. The volunteers with laboratory values within normal limits or with clinically non-significant values were called one day prior to the study for study informed consent form presentation.

All the baseline clinical and laboratory results are given in appendix 16.2.8 (Table A) and the individual clinical impression of ECG and chest X-ray (PA view) have been appended as appendix 16.2.8 (Table C). All the laboratory results, which were outside the Reference range but within the 'acceptable limit (For Acceptable limits refer Appendix V of protocol) were considered clinically non significant. There were few values as given below, which were outside the acceptable limits, however since the results were considered clinically non-significant based on clinical correlation, these subjects were included in the study.

Subject No.	Laboratory Parameter	Results	Reference Range
07	Triglycerides	191.6 mg/dL	< 150.0 mg/dL
10	Hematocrit	34.9%	40.0 – 50.0%
13	Triglycerides	231.0 mg/dL	< 150.0 mg/dL
	GGT	49.2 U/L	5.0 – 40.0 U/L
18	Lymphocytes	50%	20 – 40%
24	SGPT	40.1 U/L	4.0 – 36.0 U/L
27	Triglycerides	174.9 mg/dL	< 150.0 mg/dL

Only those volunteers who signed the study informed consent form were checked in for the study on the day of check-in (one day prior to dosing).

All the volunteers were found negative for breath alcohol test and urine test for drugs of abuse test [Cocaine (COC), Amphetamines (AMP), Marijuana (THC), Morphine (MOP), Barbiturates (BAR) and Benzodiazepine (BZO)].

Volunteers were given the rank orders based on their reporting time to the facility on pre-study day. Based on their rank orders and depending on the compliance to the requirements of the protocol, subject numbers were allotted serially. Thirty fit and consenting subjects fulfilling inclusion/ exclusion criteria and complying with the requirements of the protocol were enrolled in the study.

9.3.1 Inclusion Criteria

Subjects had to fulfill all of the following criteria to be considered for inclusion into this study:

1. Healthy volunteers within the age range of 18 to 45 years.
2. Presently non-tobacco users (smokers and chewers).
3. Willingness to provide written informed consent to participate in the study.
4. Body-mass index (BMI) between 18.50 kg/m^2 and 29.99 kg/m^2 (both inclusive) with body weight not less than 50 kg (for males) and with body weight not less than 45 kg (for females).
5. Absence of significant disease or clinically significant abnormal laboratory values or laboratory evaluation, medical history or physical examination during the screening.
6. Have a normal 12-lead ECG or one with abnormality considered to be clinically insignificant.
7. Have a normal chest X-ray PA view or one with abnormality considered to be clinically insignificant.

8. Comprehension of the nature and purpose of the study and compliance with the requirement of the distributed ICF.
9. Volunteer is regularly menstruating / Volunteer is in postmenopausal phase for at least 1 year / is surgically sterile (for females).
10. Volunteer of child bearing potential practicing an acceptable method of birth control for the duration of the study as judged by the investigator(s) such as condoms, foams, jellies, diaphragm and intrauterine device (IUD) or abstinence etc. except hormonal contraceptives (for females).

9.3.2 Exclusion Criteria

The subjects were to be excluded based on the following criteria:

1. Personal history of allergy or hypersensitivity to Montelukast or allied drugs.
2. Any major illness in the past 90 days or any clinically significant ongoing chronic medical illness e.g. Congestive Cardiac Failure (Heart failure), Hepatitis, Hypotensive episodes, Hyperglycemia etc.
3. Presence of any clinically significant abnormal values during screening e.g. significant abnormality of liver function test, renal (kidney) function test etc.
4. Severe cardiac, renal or liver impairment, gastro-intestinal disease or other conditions, any other organ or system impairment.
5. History of seizures, epilepsy or any kind of Neurological disorders.
6. Past history of Anaphylaxis or angioedema.
7. Presence of disease markers of HIV or Hepatitis B or Hepatitis C virus.
8. History of chronic consumption of any kind of alcoholic beverages for more than 2 years or having consumed alcohol within 48 hours prior to dosing.
9. Consumption of products containing xanthine derivatives (chocolates, tea, coffee or cola drinks) or tobacco products within 48 hours prior to dosing.
10. Consumption of grapefruit or grapefruit containing products or any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meats within 7 days of investigational product administration.
11. Use of any recreational drug or a history of drug addiction.
12. Participation in any clinical trial within the past 90 days.
13. History of difficulty with donating blood or difficulty in accessibility of veins in left or right arm.
14. Donation of blood (one unit or 350 mL) within 90 days prior to receiving the first dose of study medication.
15. Consumption of any other prescription drug or over the counter (OTC) drugs (including vitamins and medicinal products from natural origin) within two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last four weeks.
16. An unusual diet for whatever reason e.g. low sodium diet, for two weeks prior to receiving any medication and throughout subject's participation in the study.

17. Recent history of dehydration from diarrhoea, vomiting or any other reason within a period of 48 hours prior to the study.
18. Known hypersensitivity to heparin.
19. Use of oral contraceptive in last 90 days (for females).
20. Pregnant / lactating volunteers (for females).

9.3.3 Removal of Subjects from Therapy or Assessment

The subjects were free to withdraw from the study at any time without having to give any reasons thereof. The Principal Investigator, at his discretion, could also withdraw the subject from the study for any of the valid reason, which he deems to be appropriate in view of the safety and well being of subject, GCP principles or objectives of the project, in particular for:

1. If the subject suffers from significant illness.
2. If the subject requires concomitant medications which may interfere with pharmacokinetic of the study drug.
3. If the subject has entered the study in violation of the inclusion and the exclusion criteria.
4. If the subject is found to be non co-operative.
5. If the subject decides to voluntarily dropout from the study.

In any of these cases the compensation to the subject would have been made as per the guidelines regarding these i.e. ICH-GCP and National guidelines (ICMR guidelines for Clinical Trials) and as per the compensation structure approved by IEC.

Whatever reason if a subject would not satisfactorily completed the study would be asked to attend for the post-study examination. Whenever possible, the post-withdrawal follow up would be done immediately after the subject is withdrawn. In case a subject is not willing to undergo such medical examination, it would be documented so.

9.4 Treatments

9.4.1 Treatments Administered

An oral dose of Reference product (R) or Test product (T) was administered with 240 mL (about 8 oz) of drinking water at room temperature as per the randomization schedule under the supervision of the Medical Officer where end time of the dosing was recorded in investigational product administration forms. Subjects received the 'treatments' in such a way that each subject completing the study received both the 'treatments' test and reference at the end of the study.

Owing to the sensitivity of montelukast to light, dosing was done under yellow monochromatic light.

Subjects were dosed while in sitting posture and were instructed to remain seated or be ambulatory (avoiding any strenuous activity) for first two hours following the investigational product administration (except during recording of vitals). During this interval, under supervision, subjects were permitted to leave the bed for brief periods, e.g. to use the washroom facilities. Thereafter the subjects were allowed to engage only in normal activities while avoiding severe

physical exertion. However should any adverse event occur at any time during housing the subjects would be placed in an appropriate posture.

9.4.2 Identity of Investigational Product(s)

i) Test Formulation (T): Montelukast sodium chewable tablets 5 mg (each chewable tablet contains montelukast sodium 5.2 mg equivalent to montelukast 5 mg)
Batch No.: BMD8102C
Manufacturing Date: MAY 2011
Expiry Date: APR 2013
Manufactured by: Macleods Pharmaceuticals Ltd., India
Dose: 1 tablet
Mode of administration: Administered orally with 240 mL of drinking water.

ii) Reference Formulation (R): Singulair® (montelukast sodium) chewable tablets 5 mg (each tablet contains 5.2 mg montelukast sodium equivalent to 5 mg montelukast)
Lot No.: Z1257
Manufacturing Date: N/AV
Expiry Date: 09-2012
Distributed by: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ 08889, USA.
NDC-0006-0275-31
Dose: 1 tablet
Mode of administration: Administered orally with 240 mL of drinking water.

9.4.3 Method of Assigning Subjects to Treatment Groups

The subjects were assigned to the sequence either test or reference product, according to the randomization schedule.

The order of receiving test or reference product for each subject during the study was determined according to randomization schedule (generated using SAS® version 9.2).

Subject number was allocated as per the rank order of the reporting time of the subject to the clinical facility.

9.4.4 Selection of Doses in the Study

The available strength of Montelukast sodium chewable tablets is 4 mg and 5 mg. Single, oral dose of 1 chewable tablet of Singulair® (montelukast sodium) 5 mg was chosen, since it is safe (well tolerable) for healthy volunteers and was expected to provide measurable plasma concentrations and single dose study is adequate for this product's bioequivalence.

9.4.5 Selection and Timing of Dose for Each Subject

Dosing was done between 08:00 hrs to 08:28 hrs (0.00 hrs) in batch of two subjects during each period. The dosing interval between successive subjects was 2 minutes.

The test or reference products were orally administered to the subjects while in sitting posture with 240 mL (about 8 oz) of drinking water at room temperature as per the randomization schedule under the supervision of the Medical Officer followed by examination of the oral cavity.

The dose was administered after high fat breakfast. Subject started the recommended non-vegetarian breakfast at least 30 minutes prior to administration of the investigational product. The meal provided approximately 258.14 kcal from carbohydrate, 173.9 kcal from protein, and 560.88 kcal from fat with a total of approximately 992.92 kcal energy. Study subjects ate this meal in 30 minutes or less.

Fasting was continued for 4 hours post-dose, and then meals were provided at specified intervals. Drinking water was disallowed for 1 hour pre-dose and 1 hour post-dose administration, except 240 mL of drinking water during administration of the drug dose. Subsequently, drinking water was provided ad libitum.

9.4.6 Blinding, Packaging and Labeling

This study comprised of a randomized, open label design. Study Monitors and subjects involved in the study were not blinded. However the analyst concerned, were blinded to the sequence of administration of test or reference products to the individual subject. The plasma sample storage vials were labeled; mentioning study number, period number, subject number, sample number, time point (hrs), and aliquot number, but the identity of product administered was not mentioned. The randomization schedule was in the custody of principal investigator and the investigational product dispensing raw data record was under lock and key until the completion of statistical analysis.

An adequate number of investigational products (IPs) in sealed condition along with certificate of analysis (COA) were received at Bioequivalence department of Macleods by the registered pharmacist.

Dispensing:

As per the randomization schedule, the registered pharmacist prepared the doses under the supervision of trained personnel and in the presence of quality assurance personnel in both the periods. Owing to the sensitivity of montelukast to light, dispensing of the investigational product was done under yellow monochromatic light. Remaining investigational products were stored in their original container as retention samples in stability chamber at 22 ± 2°C and 60 ± 5% RH.

The dispensed investigational products were transferred to the drug-dispensing containers as unit doses. The IP dispensing containers used for dispensing were properly labelled for the study number, period number, subject number, treatment code, batch/ lot number, initial and date of the person dispensing the product. The IP dispensing containers along with duplicate label (similar to that stuck on the dispensing container) were placed in zip lock bag.

Investigational product accountability included the records of the receipts, intake of investigational products during both the periods of the study and remaining quantities of investigational products.
The investigational products are stored in stability chamber at 22 ± 2°C and 60 ± 5% RH and inventory are maintained in the logbook of investigational product. Data for temperature and humidity was monitored and recorded regularly through data logger.
Only authorized personnel has access to the investigational product storage areas.
For certificate of analysis of test and reference products, refer appendix – 16.1.12.

9.4.7 Prior and Concomitant Therapy

Receipt of any other prescription drug or over the counter products (including vitamins and medicinal products from natural origin) within two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last four weeks was an exclusion criterion. Further, the subjects were not supposed to consume any medication during the conduct of the study. All subjects, who checked-in the study, confirmed that they did not consume any medication within the 2 weeks of the start of first period or during the study.

9.4.8 Treatment Compliance

Subjects were provided with the identity card (I-card). While dosing, the staff on duty confirmed the subjects identity with I-card and the information mentioned on the investigational product administration form.
After administration of the dose of investigational product, examination of the oral cavity was performed under supervision of medical officer to assess the compliance to this procedure and the same was noted in the investigational product administration form of each subject. An additional label was affixed to the investigational product administration form in the appropriate place to confirm correct administration of IP. The time of actual dose administration was recorded in the investigational product administration form.
IP accountability record and evaluation of the plasma drug concentration of the samples confirmed 100% compliance of the all the subjects from whom the data were analyzed.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed

Efficacy Measurements Assessed

The following pharmacokinetic parameters (variables) of montelukast were estimated after drug administration under fed conditions:

Primary Efficacy Variables

C_{max}, AUC_{0-t} and $AUC_{0-\infty}$

Secondary Efficacy Variables

$T_{1/2}$, K_{el} and T_{max}

These parameters were derived individually for each subject from their montelukast concentration in plasma. Actual time of blood collection was considered for pharmacokinetic calculations.

For estimation of PK parameters, concentrations that were below level of quantification (BLQ) were assigned a value of zero if they preceded quantifiable samples in the initial portion of the profile. A BLQ that occurred at the end of the profile was set to zero. A BLQ or zero concentration that was embedded between two quantifiable points was assigned a value of missing. If consecutive BLQs in the terminal portion of the profile were followed by quantifiable determinations, these quantified values were excluded from PK analysis by assigning them a value of missing. In the calculations of PK parameters, missing values was ignored. Plasma concentrations used to determine PK parameters would be listed.

The pharmacokinetic parameters were calculated by non-compartmental methods using SAS® version 9.2

The calculations of the individual pharmacokinetic parameters were carried out as follows:

C_{max} : Maximum measured plasma concentration following each treatment.

AUC_{0-t} : The area under the plasma concentration versus time curve from time zero to the last measurable concentration, as calculated by the linear trapezoidal method.

$AUC_{0-\infty}$: The area under the plasma concentration versus time curve, from zero to infinity.

$AUC_{0-\infty}$ is calculated as the sum of the AUC_{0-t} plus the ratio of the last measurable concentration to the elimination rate constant.

T_{max} : Time of maximum measured plasma concentration. If maximum value occurs at more than one point, T_{max} is defined as the first point with this value in each period.

K_{el} : Apparent first order elimination or terminal rate constant calculated from semi log plot of the plasma concentration versus time curve. The parameters were calculated by linear least square regression analysis using at least the last three non-zero plasma concentration.

$T_{1/2}$: Time required for the plasma drug concentration to decrease to one half.

Safety Measurements Assessed

Safety was evaluated by monitoring clinical adverse events during study periods. Vital signs and subject questionnaire was done at the time of check-in, pre-dose and at 2.00, 5.00, 9.00, 24.00 and 32.00 hours post-dose (Time points being relative to the investigational product dosing). Medical examinations were carried out at the time of check in, check out and 32.00 of the study period.

Subjects were monitored for adverse events, if any, throughout the course of the study by asking them if they were feeling fine or had any discomfort at the time of clinical examination and recording of vital signs and recording the same in their respective CRF. The following evaluations were done at screening and in the follow-up phase:

- Medical examination (vital signs, 12 lead ECG, general and systemic examination).
- Clinical laboratory tests (haematology, clinical biochemistry) and urine analysis (only during pre-study screening).

9.5.2 Appropriateness of Measurements

The plasma samples of subjects were analyzed by a validated LC-MS/MS method. The limit of quantification of 3.00 ng/mL for Montelukast was enough to quantify the analyte from the plasma samples collected up to 32.00 hours after drug administration. The linearity range of 3.00 ng/mL to 1011.51 ng/mL for montelukast was enough to quantify the expected concentration range of montelukast from subject plasma with the proposed dose of 5 mg of Montelukast Sodium.

9.5.3 Primary Efficacy Variable(s)

The following pharmacokinetic parameters were assessed as primary efficacy variables, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$

1.	Peak plasma concentrations	C_{max}
2.	Area under plasma concentration-Time curve from time of administration until the time of last quantifiable concentration	AUC_{0-t}
3.	Area under plasma concentration-Time curve up to infinity	$AUC_{0-\infty}$

9.5.4 Drug Concentration Measurements

Concentration of montelukast was measured in plasma samples of the subjects. Blood samples (1 × 5 mL) were collected in 5 mL blood collection tube containing K_2EDTA as anticoagulant. The venous blood samples were withdrawn pre-dose and at 0.33, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00 and 32.00 hours post dose (time points being relative to the investigational product dosing).

Post-dose samples up-to 24.00 hrs collected through an indwelling cannula placed in a forearm vein. The pre-dose samples were collected within one hour prior to investigational product dosing. The post-dose samples up to 24.00 hours in house stay were collected within 2 minutes of the scheduled time where the end time of collection to the nearest minute was recorded. Similarly the post-dose samples during ambulatory visit were collected by direct prick using disposable syringe and needle within one hour of the scheduled time where the end time of collection to the nearest minute was recorded. However there were few deviations in this regard. Refer section 10.2 'Protocol Deviation'. During each ambulatory visit, the blood sample was collected up to two hours of specified schedule time of blood collection. No ambulatory blood sample collection was made after 2 hours of specified schedule time of blood collection for any subject.

Intravenous indwelling cannula was kept in place as long as required by injecting not more than 0.5 mL of 5 IU/mL of heparin in normal saline solution during the collection of multiple samples. The blood sample was collected after discarding the first 0.5 mL of heparinised blood from the tubing. Blood was also withdrawn from vein by using disposable syringe and needle if the cannula was blocked or the cannula is removed for other reasons.

Each blood sample (1 x 5 mL) was collected into 5 mL blood collection tube containing K_2EDTA as anticoagulant. The blood samples collected at each time point were centrifuged between 4 to 8°C at 4000 rpm for 10 minutes to separate plasma, after receiving the blood samples from all the

subjects. Blood samples were centrifuged within 30 minutes after collection of last blood sample; if there was any delay in centrifugation then samples were kept in cold condition. The separated plasma was aliquoted in duplicate in prelabelled polypropylene tubes during each period. These tubes were labeled with study number, period number, subject number, sample number, time point (hrs) and aliquot number. These tubes were then transferred to a deep freezer maintained below –50°C or colder for storage.

Owing to the sensitivity of montelukast to light, samples were collected and processed under yellow monochromatic light.

Plasma samples were withdrawn and replaced to analyze by Bio analytical section as and when required.

The investigational products were administered in fed conditions and no food was served till four hours post-dose. No fluid, except 240 mL drinking water administered with the investigational products was allowed from 1 hour pre-dose and 1 hours post-dose. The investigational products were administered to the subjects while in sitting posture. During this interval, under supervision, subjects were permitted to use the washroom facilities. Thereafter the subjects were allowed to engage only in normal activities while avoiding severe physical exertion. However if any adverse event occurs at any time during housing the subjects would be placed in an appropriate posture.

Subjects were instructed to abstain from alcohol and products containing xanthine derivatives (chocolates, tea, coffee or cola drinks) and tobacco products, for at least 48 hours, prior to dosing, for each period, and during their participation in the study. Subjects were instructed to abstain from grapefruit or grapefruit containing products or any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meats within 7 days of investigational product administration and during their participation in the study. Subjects were also instructed to abstain from an unusual diet for whatever reason e.g. low sodium diet, for two weeks prior to the first investigational product and throughout their participation in the study.

Validated LC-MS/MS method was employed for the estimation of montelukast in plasma. During estimation of montelukast in plasma quality control samples were distributed throughout each batch of study samples.

Whenever possible, samples from each subject were analyzed on the same standard curve. Samples with drug concentration greater than upper limit of the validated range of the analysis would be reanalyzed as per the standard test procedure based on method validation report.

The analysts concerned were blinded with respect to the randomization code, and as a result to the order of administration of the study medication.

9.6 Data Quality Assurance

The quality control personnel performed the quality control check of the case report forms and of all source documentation.

The Quality Assurance department of Macleods Pharmaceuticals Bioequivalence Department conducted both in process and retrospective audits of both Clinical, Bioanalytical and, Pharmacokinetic and Statistical phase of the study. The audits were conducted as per in-house

standard operating procedure as appended in appendix 16.1.10. The findings in brief were reported to the management.

The Quality Assurance statement is appended as appendix 16.1.8.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Following were the plans for statistical analysis:

- Use descriptive statistics (Number of subjects (N), mean, SD, CV, minimum, and maximum) to summarize the plasma concentrations at each time of measurement.
- For purpose of descriptive linear and semi-logarithmic plots of the mean and individual plasma concentration by scheduled sampling time provided.
- Report missing samples or unreportable concentration values as 'missing/ not reported' and document the reason for the same.
- Actual time of blood collection was considered for pharmacokinetic calculations.
- Use SAS® system version 9.2 for estimation of pharmacokinetic parameters and its statistical analysis for montelukast from their plasma concentration data.
- Report the summary statistics for all pharmacokinetic parameters for both the test and reference products. The reported parameters are the minimum, maximum, arithmetic means, median, standard deviation and the coefficient of variation for untransformed data and relevant pharmacokinetic parameters are the arithmetic means and the standard deviation for the log-transformed (natural) data.
- Analyze the log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of montelukast using an ANOVA model with main effects of sequence, subject nested within sequence, period, and formulation.
- Use a separate ANOVA model to analyze each of the parameters. Use a 5% level of significance to test significance of all effects.
- Include calculation of mean square error, coefficient of variance and the associated degree of freedom for each analysis of variance.
- Use SAS procedure 'PROC GLM' to perform analysis of variance.
- Calculate and report ratio of geometric means using the LSM for log transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
- Calculate ratio of test to reference for each subject for all relevant pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$).
- Report the geometric means of the test and reference product and express ratios of mean AUC_{0-t} to mean $AUC_{0-\infty}$ for test and reference in percentage.
- Calculate the power of the ANOVA model to detect the ratio of the two products averages (geometric means) being equal to 125% (or 80%) at the 5 % significance level for analyses using the log-transformed data.

- Calculate the coefficient of variation using $\sqrt{e^{MSE}-1}$ with help of SAS® version 9.2. Where MSE is mean squared error obtained from analysis of variance model.
- Calculate a 90% confidence interval for the ratio of both the products averages (geometric means) by first calculating the 90% confidence interval for the differences in the averages (least square means) of the log-transformed data and then taking the antilogarithms of the obtained confidence limits.
- Claim the treatment to be bioequivalent if the confidence intervals of montelukast are entirely included in the range of 80.00% – 125.00% for log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

9.7.2 Determination of Sample Size

Following data are obtained from "Published literature".[2] Based on 2 x 2 Crossover study of Montelukast 5 mg Chewable Tablets under fed condition performed on 24 Healthy subjects under fed condition; data generated from a total of 24 subjects completed in the study.

The pharmacokinetic parameters and statistical results for Montelukast is as follows:

Treatment	AUC_{0-t} (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)
Test (S.D.)	1686.3 (612.4)	1744.6 (638.2)	264.5 (96.6)	1.67 (1.33 – 5.00)	4.80
Reference (S.D.)	1826.4 (564.0)	1880.2 (586.3)	288.8 (87.5)	2.67 (1.33 – 8.00)	4.46
*** Ratio (90% CI)**	90.63% 85.84 – 95.69%	91.11% 86.49 – 95.97%	89.91% 82.69 – 97.75%	-	-
Intra-subject CV (%)	10.98%	10.52%	17.00%	-	-

* Log-transformed values

Sample size was calculated using SAS® 9.1.3. The highest Intra-subject C.V. for montelukast was observed to be 17.00%. Hence using this Intra-subject C.V. the sample size calculation is as follows:

Two-Sample Equivalence

Multiplicative Model Lower Bound = 0.80 Upper Bound = 1.25

Coefficient of Variation = 0.1700 Alpha = 0.05

Null Ratio	Power	N per Group
0.95	0.800	13
	0.850	15
	0.900	18
	0.950	22
1.00	0.800	11
	0.850	12
	0.900	14
	0.950	16
1.05	0.800	13
	0.850	15
	0.900	17
	0.950	22

The highest intra subject C.V. for montelukast was observed to be 17.00% for C_{max} (ng/mL) in the published literature. So to achieve 80% power a sample size of 13 per group was sufficient to conclude bioequivalence. Therefore accounting for dropout or withdrawal of the subjects during conducts of the study 30 healthy subjects were decided to be recruited in a crossover study design to achieve the desired sample size to conclude bioequivalence.

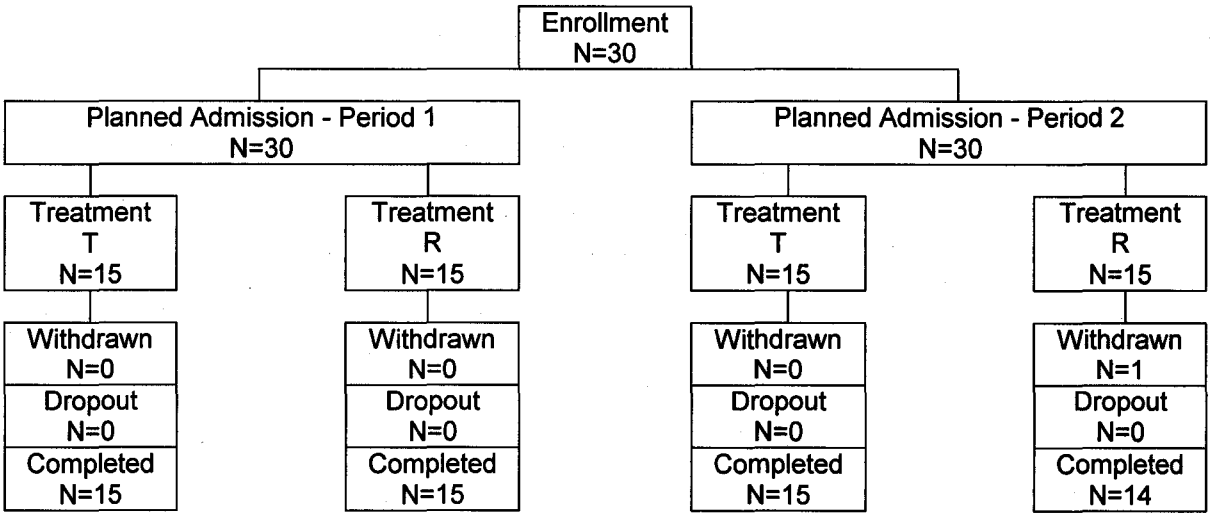
9.8 Changes in the Conduct of the Study or Planned Analyses

There were no changes in the conduct of the study or planned analysis.

10.0 STUDY SUBJECTS

10.1 Disposition of Subjects

A total number of 30 subjects were planned and enrolled. Of these 30 subjects, subject number 13 was withdrawn from the study in period 2 (post-dose) on principal investigator advice due to adverse event. Thus twenty-nine subjects completed both the periods.



10.2 Protocol Deviations

- As per the protocol clinical laboratory investigations to be done at Pathology department of Macleods Pharmaceuticals Ltd., Mumbai; while during screening dated 30th June 2011, hematology estimation for subject number 02 was done at Vaidya's Laboratory (NABL accredited) due to malfunction in CELL-DYN machine of pathology laboratory of Macleods Pharmaceuticals Ltd., Mumbai. Some extra parameters were done which were not considered for evaluation of eligibility of volunteers to enroll in the study.
- As per protocol blood samples should be collected within two minutes of scheduled time for blood collection for in-house samples. All actual times of the sample withdrawal were recorded in the bleed sheet. However, there was 01 deviation from the schedule time of the collection above the permitted deviation time in the study.

Sr. No.	Subject No.	Sample Time Point (Hrs)	Scheduled Time	Actual Time	Deviation in Hour	Reason for Deviation
Period 1						
1.	19	16.00	00.06 hrs	00.09 hrs	0.05	Cannula block

- As per protocol total 27 samples should be collected per subject in each period. However there was 01 deviation in period 1 in this regard. Sample was not collected since the subject didn't report to the facility.

Sr. No.	Time Point (Hrs)	Subject Number	
		Period 1	Period 2
1.	32.00	15	-

The above deviations were duly incorporated during pharmacokinetic analysis.

The above deviations were recorded as protocol deviations and are recorded in appendix 16.2.2.

11.0 EFFICACY EVALUATION

11.1 Data Sets Analyzed

The data of 29 completing subjects (01 to 12 and 14 to 30) receiving reference and test product were utilized for pharmacokinetic and statistical evaluations.

Subject's 13 plasma samples were excluded from the efficacy evaluation.

Plasma samples of subject number 13 were not analyzed, since the subject was withdrawn from the study.

11.2 Demographic and Other Baseline Characteristics

The demographic characteristics of the 29 subjects completed the study were as follows:

- Age between 20 and 40 years [26.7 (mean) ± 4.72 (SD) years].
- Weight between 51.3 and 75.6 kg [61.77 (mean) ± 7.264 (SD) kg].
- Height between 1.56 and 1.78 meters [1.677 (mean) ± 0.0570 (SD) meters].
- BMI between 18.52 and 27.16 kg/m^2 [21.995 (mean) ± 2.6270 (SD) kg/m^2].

The demographic characteristics of the 30 subjects recruited in the study were as follows:

- Age between 20 and 40 years [26.6 (mean) ± 4.63 (SD) years].
- Weight between 51.3 and 77.0 kg [62.28 (mean) ± 7.660 (SD) kg].
- Height between 1.56 and 1.78 meters [1.680 (mean) ± 0.0590 (SD) meters].
- BMI between 18.52 and 27.16 kg/m^2 [22.071 (mean) ± 2.6154 (SD) kg/m^2].

The demographic data is summarized in section 14.1. The demographic data for individual subjects are appended in appendix 16.2.4.

11.3 Measurements of Treatment Compliance

All the subjects took the medications as administered. Examination of the oral cavity immediately after drug administration was performed under supervision of medical officer to assess the compliance to this procedure. Further, the evaluation of the plasma drug concentration of the samples confirmed 100% compliance of the all the subjects from whom the data were analyzed. Plasma levels of montelukast in individual subjects at different time points following reference and test formulations are given in appendix 16.2.5.

11.4 Efficacy Results and Tabulations of Individual Subject Data

11.4.1 Analysis of Efficacy

The various un-transformed mean pharmacokinetic parameters estimated for both the reference and test formulations of montelukast under fed conditions are as follows:

Pharmacokinetic Parameters	Test product (N=29)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	233.264	60.4812	25.93	225.74	127.74 - 403.04
AUC_{0-t} (ng*hrs/mL)	1737.31974	466.971286	26.88	1692.5871	902.8525 - 2825.8919
$AUC_{0-\infty}$ (ng*hrs/mL)	1775.70179	479.499083	27.00	1718.5899	926.0623 - 2914.9130
T_{max} (hrs)	3.577	1.1783	32.94	3.33	2.25 - 7.00
$T_{1/2}$ (hrs)	5.09286	1.391439	27.32	5.0008	3.3454 - 7.4673
K_{el} (hr^{-1})	0.14651	0.040185	27.43	0.1386	0.0928 - 0.2072

Pharmacokinetic Parameters	Reference product (N=29)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	210.174	58.4142	27.79	208.28	99.20 - 348.87
AUC_{0-t} (ng*hrs/mL)	1689.74246	491.645807	29.10	1630.1153	751.9559 - 2691.6248
$AUC_{0-\infty}$ (ng*hrs/mL)	1729.81350	510.609852	29.52	1667.4669	768.8925 - 2794.1476
T_{max} (hrs)	3.972	1.3612	34.27	3.67	2.00 - 6.00
$T_{1/2}$ (hrs)	4.83996	1.360678	28.11	4.1772	2.9033 - 7.4256
K_{el} (hr^{-1})	0.15392	0.040440	26.27	0.1659	0.0933 - 0.2387

The summary results are tabulated in section 14.2 and the individual subjects and mean pharmacokinetic parameters for both the test and reference formulations have been tabulated in appendix 16.2.6. The statistical output and pharmacokinetic from SAS® version 9.2 is appended in appendix 16.4.1.

The ln-transformed least square mean and 90% confidence interval based on least square mean obtained from ANOVA and ratio of geometric means for the pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for montelukast under fed conditions are summarized in the following table:

Geometric mean, Ratio, Intra-Subject C.V., Power and 90 % Confidence Interval for Montelukast						
Pharmacokinetic Parameters	Geometric mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90 % Confidence Interval (%)
	Test (T)	Reference (R)				
C_{max} (ng/mL)	226.256	202.497	111.73	18.08	99.38	103.11 - 121.07
AUC_{0-t} (ng*hrs/mL)	1678.498	1620.421	103.58	8.85	100.00	99.57 - 107.76
$AUC_{0-\infty}$ (ng*hrs/mL)	1715.060	1657.176	103.49	8.86	100.00	99.48 - 107.67

ANOVA RESULTS:

Formulation Effect

Formulation effect found to be statistically significant for C_{max} & insignificant for AUC_{0-t} & $AUC_{0-\infty}$.

Sequence Effect

Sequence effect found to be statistically insignificant for C_{max}, AUC_{0-t} & $AUC_{0-\infty}$.

Period Effect

Period effect found to be statistically insignificant for C_{max}, AUC_{0-t} & $AUC_{0-\infty}$.

RATIO AND 90% CONFIDENCE INTERVAL:

The ratio of geometric mean and 90% confidence interval for the ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} & $AUC_{0-\infty}$ were found to be respectively 111.73% & 103.11% – 121.07%; 103.58% & 99.57% – 107.76% and 103.49% & 99.48% – 107.67%.

POWER AND INTRA SUBJECT VARIABILITY:

The power and intra subject variability for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} & $AUC_{0-\infty}$ were found to be respectively 99.38% & 18.08%; 100.00% & 8.85% and 100.00% & 8.86%.

11.4.2 Statistical / Analytical Issues

Statistical Issues

There were no statistical issues.

Analytical Issues

There were no analytical issues.

11.4.3 Tabulation of Individual Response Data

All individual subject concentration data that was used for pharmacokinetic analysis at each time point is appended as appendix 16.2.5. Individual plasma concentration time curves are presented in linear and log-linear scale in appendix 16.2.5.

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

In the present bioequivalence study the pharmacokinetic end points were considered for the bioequivalence conclusion and hence the pharmacodynamic was not measured. Thus the drug dose, dose concentration and relationship to response were not evaluated.

11.4.5 Drug-Drug and Drug-Disease Interactions

Not Applicable

11.4.6 By-Subject Displays

Not applicable

11.4.7 Efficacy Conclusions

The 90% confidence interval for the ratio (Test/Reference) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of montelukast were within the acceptable limits of bioequivalence 80.00% - 125.00%.

Thus it is concluded that the test product, Montelukast sodium chewable tablets 5 mg (each chewable tablet contains montelukast sodium 5.2 mg equivalent to montelukast 5 mg) manufactured by Macleods Pharmaceuticals Ltd., India is bioequivalent with the reference product, Singulair® (montelukast sodium) chewable tablets 5 mg (each tablet contains 5.2 mg montelukast sodium equivalent to 5 mg montelukast) distributed by Merck & Co. Inc., USA in healthy, adult, human subjects under fed condition.

12.0 SAFETY EVALUATION

12.1 Extent of Exposure

Twenty-nine subjects who completed the study and subject number 13 [who was withdrawn from the study in period 2 (post-dose) on principal Investigator's advice due to adverse event] were exposed to montelukast sodium 5 mg twice as per randomization schedule.

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of Adverse Events

One subject (subject number 13) experienced adverse event during conduct of the study.

On dosing day of period 2, subject number 13 had fever after 2 hours 48 minutes of dosing.

There were few out of reference range laboratory values obtained at the post-study assessment but these were not clinically significant except for subject number 01, 17, 20, 25 and 28. The details for the same are given in section 12.4.2. The clinically significant out of reference range values for the post-study examination of the subject's laboratory investigations are tabulated in 14.3.4.

12.2.2 Displays of Adverse Events

The list of adverse events occurred after initiation of the study is displayed in summary table in section 12.2.4 and the post-study clinically significant out of reference range laboratory results are listed in section 14.3.4.

12.2.3 Analysis of Adverse Events

The adverse event experienced by subject during conduct of the study was possibly related to the study drug.

The out of reference range laboratory values obtained during post-study evaluation except for that listed in section 12.2.4 were considered to be clinically non significant. The relationship of the drug to the clinically significant out of reference range laboratory values obtained during post-study evaluation is given in section 12.2.4.

12.2.4 Listing of Adverse Events by Subjects

One subject experienced adverse event during conduct of the study.

The relationship of the drug to the adverse event experienced by the subject is as mentioned below:

Sub. No.	Adverse Event	Date and Time of Last Dosing	Date and time of Occurrence	Time of AE since Last Dose	Date and time of Resolution	Duration of AE (From Occurrence to Resolution)	Relationship with the Study Drug	Treatment Received (Sequence)
13	Fever	21st July 2011 08:24 hrs	21st July 2011 11:12 hrs	2 hours 48 minutes	22nd July 2011 15:00 hrs	27 hours 48 minutes	Unlikely	R (TR)

The relationship of the drug to the clinically significant out of reference range laboratory values obtained during post-study evaluation is as mentioned below:

Subject Number	Laboratory Parameter	Safety Assessment Results	Reference Range	Remark	Relationship with the Study Drug
01	Haemoglobin	11.1 g/dL	13.0 – 17.0 g/dL	Decreased	Unlikely
	Hematocrit	32.7%	40.0 – 50.0%		
17	Leucocyte Count	13.60 x 1000/µL	4.00 – 10.00 x 1000/µL	Increased	Unlikely
20	Leucocyte Count	12.10 x 1000/µL	4.00 – 10.00 x 1000/µL	Increased	Unlikely
25	Haemoglobin	11.2 g/dL	13.0 – 17.0 g/dL	Decreased	Unlikely
	Hematocrit	33.3%	40.0 – 50.0%		
28	SGOT	160.0 U/L	4.0 – 36.0 U/L	Increased	Unlikely
	SGPT	299.2 U/L	8.0 – 33.0 U/L		

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

There were no serious adverse events reported in the study.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subjects and Each Abnormal Laboratory Value

Listed in appendix 16.2.8 are the various biochemical, hematological and urine sample assessment for the subjects, pre and post-clinical phase. The clinically significant out of reference range values for the post-study examination of the subject's laboratory investigations are tabulated in 14.3.4.

12.4.2 Evaluation of Each Laboratory Parameter

There were few out of reference range laboratory values obtained at the post-study assessment, but these were not clinically significant except for subject number 01, 17, 20, 25 and 28 who showed clinically significant post-study out of reference range laboratory value.

All the post-study safety assessment clinical and laboratory results are given in appendix 16.2.8, 'Listing of Individual Laboratory Parameters by Subject' [B- Laboratory Tests Report (Post-study safety Assessment)]. All the laboratory results, which were outside the reference range but within the 'acceptable limit', (for acceptable limit refer IEC approved Protocol, appendix V) were not considered clinically significant. There were few values as given below, which were outside the acceptable limits, however not considered clinically significant based on the clinical co-relation and have not been included as adverse events. For subject number 01, 17, 20, 25 and 28 the laboratory result outside acceptable range are considered as clinically significant based on the clinical co-relation and are reported as adverse events.

Subject No.	Laboratory Parameter	Safety Assessment Results	Baseline Results	Reference Range	Remark
01	Haemoglobin	11.1 g/dL	12.0 g/dL	13.0 – 17.0 g/dL	Clinically significant
	Hematocrit	32.77%	39.4%	40.0 – 50.0%	
	Triglycerides	215.3 mg/dL	63 mg/dL	<150.0 mg/dL	Clinically not significant
02	Triglycerides	246.8 mg/dL	121.8 mg/dL	<150.0 mg/dL	Clinically not significant
03	Triglycerides	314.7 mg/dL	111.2 mg/dL	<150.0 mg/dL	Clinically not significant
04	Total Cholesterol	239.7 mg/dL	217.8 mg/dL	<200.0 mg/dL	Clinically not significant
	Triglycerides	211.3 mg/dL	138.7 mg/dL	<150.0 mg/dL	
05	Triglycerides	215.3 mg/dL	91.5 mg/dL	<150.0 mg/dL	Clinically not significant
06	Triglycerides	232.8 mg/dL	123.7 mg/dL	<150.0 mg/dL	Clinically not significant

Subject No.	Laboratory Parameter	Safety Assessment Results	Baseline Results	Reference Range	Remark
07	Lymphocytes	10%	35%	20 – 40%	Clinically not significant
	Triglycerides	269.5 mg/dL	191.6 mg/dL	<150.0 mg/dL	Clinically not significant
08	Triglycerides	301.7 mg/dL	102.4 mg/dL	<150.0 mg/dL	Clinically not significant
10	Triglycerides	244.8 mg/dL	78.1 mg/dL	<150.0 mg/dL	Clinically not significant
11	Triglycerides	177.0 mg/dL	102.8 mg/dL	<150.0 mg/dL	Clinically not significant
12	Triglycerides	413.0 mg/dL	155.3 mg/dL	<150.0 mg/dL	Clinically not significant
13	Triglycerides	182.9 mg/dL	231.0 mg/dL	<150.0 mg/dL	Clinically not significant
	GGT	58.5 U/L	49.2 U/L	5.0 – 40.0 u/L	
14	Triglycerides	183.4 mg/dL	128.4 mg/dL	<150.0 mg/dL	Clinically not significant
16	Triglycerides	309.5 mg/dL	109.0 mg/dL	<150.0 mg/dL	Clinically not significant
17	Leucocyte Count	13.60 x 1000/µL	9.66 x 1000/µL	4.00 – 10.00 x 1000/µL	Clinically significant
	Triglycerides	223.4 mg/dL	73.4 mg/dL	<150.0 mg/dL	Clinically not significant
19	Triglycerides	166.9 mg/dL	92.3 mg/dL	<150.0 mg/dL	Clinically not significant
20	Leucocyte Count	12.10 x 1000/µL	9.35 x 1000/µL	4.00 – 10.00 x 1000/µL	Clinically significant
	Triglycerides	279.2 mg/dL	95.0 mg/dL	<150.0 mg/dL	Clinically not significant
21	Triglycerides	270.2 mg/dL	67.3 mg/dL	<150.0 mg/dL	Clinically not significant
23	Triglycerides	185.9 mg/dL	102.5 mg/dL	<150.0 mg/dL	Clinically not significant
24	ESR	25 mm/hr	2 mm/hr	<15 mm/hr	Clinically not significant
	Triglycerides	215.0 mg/dL	101.0 mg/dL	<150.0 mg/dL	
25	Haemoglobin	11.2 g/dL	12.1 g/dL	13.0 – 17.0 g/dL	Clinically significant
	Hematocrit	33.3%	36.9%	40.0 – 50.0%	
26	Hematocrit	34.5%	36.6%	40.0 – 50.0%	Clinically not significant
27	Leucocyte Count	11.40 x 1000/µL	8.91 x 1000/µL	4.00 – 10.00 x 1000/µL	Clinically not significant
	Triglycerides	259.3 mg/dL	174.9 mg/dL	<150.0 mg/dL	
28	SGPT	160.0 U/L	18.0 U/L	4.0 – 36.0 U/L	Clinically significant
	SGOT	299.2 U/L	21.1 U/L	8.0 – 33.0 U/L	
29	Triglycerides	184.2 mg/dL	72.9 mg/dL	<150.0 mg/dL	Clinically not significant

Note: The triglyceride levels of subjects are out side acceptable limit. Since the post-study safety assessment samples were collected post-prandially, the triglyceride levels are bound to be high and therefore raised triglyceride levels are clinically acceptable.

The clinically significant out of reference range values for the post-study examination of the subject's laboratory investigations are tabulated in 14.3.4.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Laboratory assessments, including urine test for drugs of abuse and alcohol breath test were carried out prior to the study.

In the pre-study assessments, all out of range clinical laboratory values were clinically acceptable, for the subjects enrolled in the study.

The post-study clinically significant out of reference range laboratory parameters are summarized in the 14.3.4 and the individual recording of laboratory parameters are appended in appendix 16.2.8 (Table B).

Vital signs and subject questionnaire was done at the time of check-in, pre-dose and at 2.00, 5.00, 9.00, 24.00 and 32.00 hours post-dose (Time points being relative to the investigational product dosing).

Medical examinations were carried out at the time of check-in, check out and at 32.0 hrs post dose. The individual recording of vital signs for both the periods has been appended as appendix 16.2.8 (Table D).

All the subjects enrolled and dosed had clinically acceptable vital signs values.

A medical officer was available within the clinical facility whenever the subjects were housed (from check-in to checkout).

At the end of the study period, post-study safety assessments of the subjects completing the study were carried out which included: Medical examination including recording of vital signs [Blood Pressure (BP), Pulse and Temperature], general examination, physical and systemic examination. 12-lead ECG for heart rate, rhythm and specific finding (if any). Laboratory parameter investigation including complete blood count – erythrocyte count, platelet count, haemoglobin, hematocrit, leucocyte count, ESR and differential leucocyte count (DLC); Biochemistry –blood sugar (random), total cholesterol and triglycerides; Hepatic profile – SGOT, SGPT, GGT, alkaline phosphatase and serum bilirubin (total, direct, indirect), Renal profile – serum creatinine, BUN, calcium, electrolytes (sodium, potassium, chlorides).

No clinically significant abnormalities in ECGs were reported in subjects during post-study safety assessments. The individual clinical impression of ECG has been appended as appendix 16.2.8 (Table C).

Laboratory values outside the reference range were considered clinically not significant based on clinical co-relation and have not been included as adverse events except for few subjects as given in section 12.4.2. The clinically significant out of reference range values for the post-study examination of the subject's laboratory investigations are tabulated in 14.3.4 and the individual recordings of laboratory parameters are appended in appendix 16.2.8 (Table B).

12.6 Safety Conclusions

No serious adverse event occurred during the conduct of the study.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

A total of 30 subjects were planned and enrolled. Of these 30 subjects 29 subjects completed the study. Single dose administration of Montelukast sodium chewable tablets 5 mg was well tolerated and no new safety issues were identified during the study. There were few clinically relevant changes in laboratory safety variables for five subjects which were unlikely related to the study drug. No subject discontinued study treatment due to adverse event. No deaths, serious adverse events or adverse events classified as 'other significant AEs' occurred during the study.

The plasma samples of all the subjects who completed the study were analyzed for montelukast concentration level. Plasma concentration of twenty-nine subjects who completed the study was utilised for pharmacokinetic and statistical evaluations.

The mean plasma concentration time profiles of montelukast for the two treatments are shown in Figure 1 and 2 (Refer section 14.2 'Efficacy Data').

After oral administration of the reference product under fed condition the drug was rapidly absorbed and median t_{max} was 3.67 hrs where for other PK parameters mean C_{max} 210.174 ng/mL (range 99.20 - 348.87 ng/mL), AUC_{0-t} 1689.74246 ng*hrs/mL (range 751.9559 - 2691.6248 ng*hrs/mL) and $AUC_{0-\infty}$ 1729.81350 ng*hrs/mL (range 768.8925 - 2794.1476 ng*hrs/mL).

After oral administration of the test product under fed condition the drug was rapidly absorbed and median t_{max} was 3.33 hrs where for other PK parameters mean C_{max} 233.264 ng/mL (range 127.74 - 403.04 ng/mL), AUC_{0-t} 1737.31974 ng*hrs/mL (range 902.8525 - 2825.8919 ng*hrs/mL) and $AUC_{0-\infty}$ 1775.70179 ng*hrs/mL (range 926.0623 - 2914.9130 ng*hrs/mL).

Bioequivalence was assessed using standard equations. The 90% confidence intervals for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for montelukast were within the usual acceptable limit for 80.00-125.00%.

In summary, the test formulation is bioequivalent to the reference in terms of both the rate and extent of absorption.

Both the formulations are well tolerated following a single dose administration of the investigational product.

14.0 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Demographic Data of Subjects Recruited in the Study:

	Age (Yrs)	Height (m)	Weight (kg)	BMI (kg/m2)
Number	30	30	30	30
Median	25.00	1.69	60.85	21.67
Mean	26.6	1.680	62.28	22.071
Standard Deviation	4.63	0.0590	7.660	2.6154
Minimum	20	1.56	51.3	18.52
Maximum	40	1.78	77.0	27.16

Demographic Data of Subjects Completed the Study

	Age (Yrs)	Height (m)	Weight (kg)	BMI (kg/m2)
Number	29	29	29	29
Median	25.00	1.68	60.80	21.66
Mean	26.7	1.677	61.77	21.995
Standard Deviation	4.72	0.0570	7.264	2.6270
Minimum	20	1.56	51.3	18.52
Maximum	40	1.78	75.6	27.16

14.2 Efficacy Data

Summary statistics of pharmacokinetic parameters for montelukast after administration of single dose montelukast sodium chewable tablets 5 mg in 29 healthy, adult human subjects under fed conditions.

Product/Statistics	C_{max} (ng/mL)	AUC_{0-t} (ng*hrs/mL)	$AUC_{0-\infty}$ (ng*hrs/mL)
Untransformed Reference Product (R)			
Arithmetic Mean	210.174	1689.74246	1729.81350
S.D.	58.4142	491.645807	510.609852
C.V. %	27.79	29.10	29.52
N	29	29	29
Test Product (T)			
Arithmetic Mean	233.264	1737.31974	1775.70179
S.D.	60.4812	466.971286	479.499083
C.V. %	25.93	26.88	27.00
N	29	29	29
Ratio of Arithmetic Mean (% Bioavailability)			
T/R (%)	110.99	102.82	102.65
Ratio (%) for Mean AUC_{0-t} to Mean $AUC_{0-\infty}$			
Reference		97.68	
Test		97.84	
Log Transformed (Natural Log) Least Square Mean			
Reference	5.311	7.390	7.413
Test	5.422	7.426	7.447
Geometric Mean			
Reference	202.497	1620.421	1657.176
Test	226.256	1678.498	1715.060
Ratio of geometric Mean			
T/R (%)	111.73	103.58	103.49
90 % Confidence Interval (T/R)			
Lower limit (%)	103.11	99.57	99.48
Upper limit (%)	121.07	107.76	107.67
Power (%)	99.38	100.00	100.00
D.F.	27	27	27
Intra Subject C.V. (%)	18.08	8.85	8.86
Mean Square Error (MSE)	0.032172	0.007803	0.007821
P-value (ANOVA) for ln-transformed data			
Formulation	0.0261	0.1409	0.1511
Period	0.4860	0.7538	0.7898
Sequence	0.4528	0.3702	0.3825

Figure 1

Comparative Linear Plot of Montelukast Mean Plasma Concentration (ng/mL) Vs Time (Hour)(N=29)

subject=MEAN

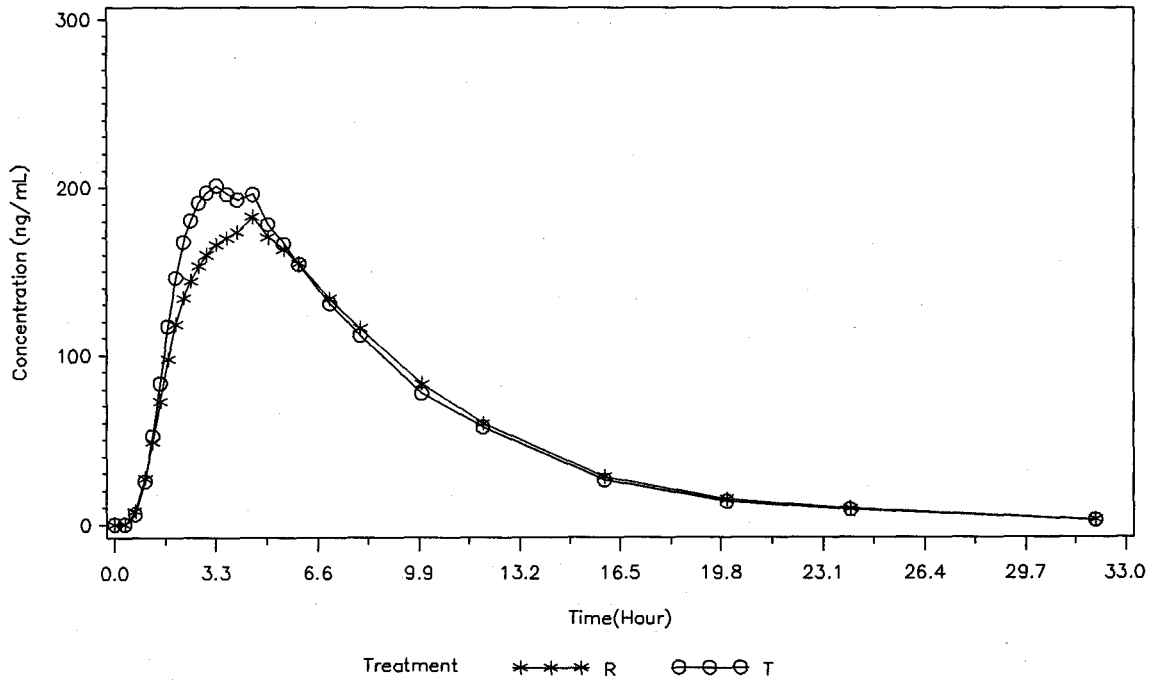
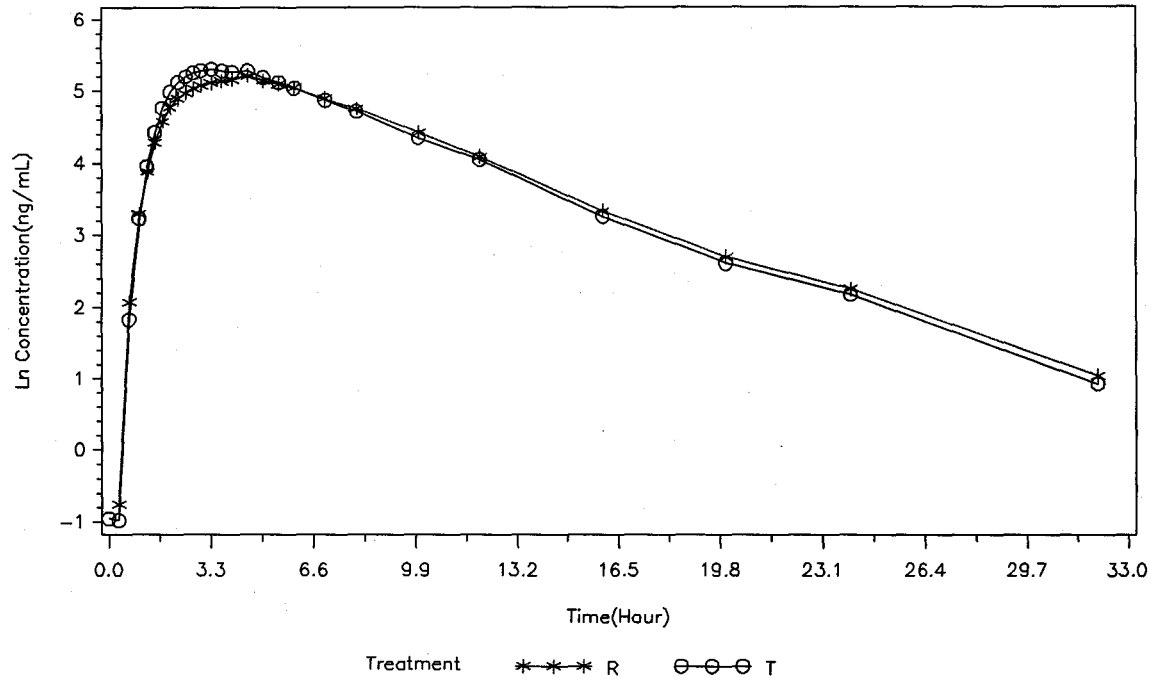


Figure 2

Comparative Semi Log Plot of Montelukast Mean Plasma Concentration (ng/mL) Vs Time (Hour)(N=29)

subject=MEAN



14.3 Safety Data

14.3.1 Display of Adverse Events

One subject (subject number 13) experienced adverse event during conduct of the study.

Five subjects (subject number 01, 17, 20, 25 and 28) enrolled in the study were found to have clinically significant post-study laboratory values. The list of clinically significant post-study out of reference range laboratory values is listed in section 14.3.4.

The detailed description of the adverse events and their handling are given in appendix 16.2.7.

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

No deaths or other serious adverse events or any other significant adverse events were observed in the study.

14.3.3 Narrative of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable

14.3.4 Abnormal Laboratory Value Listing

Following table gives details of outside acceptable limit findings, which are clinically significant in laboratory test of subjects post-study.

Subject Number	Laboratory Parameter	Reference Range	Safety Assessment Results	Follow-up Result	Comments
01	Haemoglobin	13.0 – 17.0 g/dL	11.1 g/dL	Not done	Lost for follow-up
	Hematocrit	40.0 – 50.0 %	32.7%		
17	Leucocyte Count	4.00 – 10.00 x 1000/µL	13.60 x 1000/µL	Not done	Lost for follow-up
20	Leucocyte Count	4.00 – 10.00 x 1000/µL	12.10 x 1000/µL	Not done	Lost for follow-up
25	Haemoglobin	13.0 – 17.0 g/dL	11.2 g/dL	Not done	Lost for follow-up
	Hematocrit	40.0 – 50.0%	33.3%		
28	SGOT	4.0 – 36.0 U/L	160.0 U/L	Not done	Lost for follow-up
	SGPT	8.0 – 33.0 U/L	299.2 U/L		

15.0 REFERENCE LIST

(Refer appendix – 16.1.12 'Important Publications Referenced in the Report')

1. U.S. Food and Drug Administration-Drug product label of Singulair®, (NDA) 020830, approved on 27/04/2011 Cited on 08/06/2011 Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020829s57, 020830s059, 021409s034lbl.pdf
2. Public Assessment Report Scientific discussion Montelukast "Teva" Chewable Tablets 4 mg and 5 mg. Cited on 16/02/2011 Available from: http://www.hma.eu/filedmin/dateien/pipar/dk1104/parmod5_dk1104_montelukastteva.pdf